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ARTICLE

Genetic and non-genetic factors influencing efavirenz population pharmacokinetics among human immunodeficiency virus-1-infected children in Ethiopia

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Abstract

Despite the potential for efavirenz (EFV) to be an effective alternative antiretroviral agent, its sources of wide inter- and intra-individual pharmacokinetic (PK) variability are not well-characterized in children. We investigated the effects of genetic and non-genetic factors, including demographic, treatment duration, baseline clinical, and biochemical characteristics, on the PKs of EFV through population-PK modeling. Antiretroviral therapy (ART) naïve HIV infected children, 3–16 years (n = 100), were enrolled in Ethiopia and received EFV-based combination ART. EFV concentrations after the first dose and at steady-state collected over a span of 1 year were modeled using population-based methods. A one-compartment model with first-order absorption kinetics described the observed EFV data adequately. The *CYP2B6*6* and *ABCB1c.4036A>G* genotypes were identified as major factors influencing EFV clearance. The typical estimates of oral clearance, volume of distribution, and absorption rate constant for typical 22 kg children with *CYP2B6 *1/*1* and *ABCB1c.4036G/G* genotypes were 4.3 L/h, 124 L, and 0.776/h, respectively. Clearance was reduced by 28% and 72% in *CYP2B6*1/*6* and *CYP2B6*6/*6* genotypes, respectively. Compared to week 1, clearance was higher from weeks 8 and 12 in *CYP2B6*1/*6* and *CYP2B6*1/*1* genotypes, respectively. Simulations indicated that EFV 12-h concentrations were comparable across weight bands, but more than 80% of subjects with *CYP2B6*6/*6* had EFV concentrations greater than 4 μg/mL. EFV PK variability among children is partly explained by body weight, treatment duration, *CYP2B6*6*, and *ABCB*1 rs3842 genotypes. Therefore, in addition to body weight, pediatric dosing of EFV should consider pharmacogenetic variability, duration of therapy, and individual treatment outcomes.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Efavirenz (EFV) is one of the highly effective anti-HIV drugs, but it has wide inter- and intra-individual variability in its pharmacokinetics (PKs) and hence treatment outcomes.

WHAT QUESTIONS DID THIS STUDY ADDRESS?

This study describes a population PK model of EFV in Ethiopian children and establishes the sources of EFV PK variability in this population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study identifies important genetic and non-genetic factors influencing EFV PKs and compares its exposures across dosing weight bands in the Ethiopian children.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The study supports the use of genotype and weight-based dosing of EFV in children. In addition, the study encourages management of EFV dosage based on treatment outcome.

INTRODUCTION

Efavirenz (EFV) is a potent non-nucleoside inhibitor of the human immunodeficiency virus-1 (HIV-1) reverse transcriptase that plays a key role in the fight against the HIV pandemic. The recent literature review, based on 156 publications from 68 clinical trials that informed previous World Health Organization (WHO) guidelines, shows that low-dose EFV-based combination antiretroviral treatment (cART) regimens are still alternatives to the recently introduced and preferred dolutegravir-based regimen.[1] Use of low-dose EFV among the pediatric population is not well supported by previous studies, especially in sub-Saharan countries where the disease burden is very high. The current WHO recommendations propose use of EFV for special circumstances, whereas some study favors use of EFV-based cART for children due to proven safety, convenience, and potent inhibition of HIV-1.[2,3] Given the available evidence that support lower doses of EFV compared to the currently used doses, the neuropsychological incidents associated with EFV can be mitigated.

The EFV pharmacokinetics (PKs) are characterized by a long steady-state half-life permitting once-a-day dosing.[4] EFV is known to induce its own metabolism by increasing the expression of cytochrome P450 enzymes.[5,6] Cytochrome P450, specifically CYP2B6, is the predominant enzyme that metabolizes EFV.[7,8] The relevant CYP2B6 variant allele that affects plasma EFV concentration includes *CYP2B6 c.516G>T*, *c.785A>G*, and *c.983T>C*, which have been widely characterized across the world populations.[9] The *CYP2B6*6* (*c.516G>T* linked with *c.785A>G*) variant allele is associated with decreased enzyme activity and the corresponding increase in the incidence of EFV-linked neuropsychological toxicity.[10,11] Other studies show that the *CYP2B6* gene polymorphisms implicated for the wide inter- and intra-individual variability in EFV exposure in the adult population necessitated consideration of dosing optimizations for EFV.[12,13] The results of the PK and pharmacogenetic studies of EFV in adult African and Asian populations show that lower doses of EFV than the previously prescribed dose are enough for effective control of HIV-1.[13,14] Gene polymorphism of CYP2B6 is also implicated for inter- and intra-individual variabilities of EFV PKs among the pediatric population as well.[15–17] Besides the CYP2B6 gene polymorphism, other gene polymorphism implicated for interindividual variability of EFV PKs are in the *CYP2A6* gene,[18–20] the *UGT2B7* gene,[18] and the *ABCB1* gene.[21–23] However, the reports indicate that the impact of these gene polymorphisms are inconsistent and play minor roles.

Population PK modeling and simulation is becoming popular worldwide due to its applicability for the study of PK parameters in pediatrics where intensive sampling may not be feasible and therefore, PK samples are sparse and/or unavailable. Most of the time, intensive samplings are not possible primarily due to ethical and practical reasons. The optimal use of limited pediatrics data during drug development and treatment optimization of existing medications is the best way to address these challenges. The population-based approach, which integrates pharmacogenetic and PK studies, is suitable to capture possible contributors of variability of the PK parameters. Population-based PK and pharmacogenetic analysis on EFV have been reported in the literature for adults and children worldw ide.[9,12,15–17,24–26] However, there are limited reports for

children in sub-Saharan Africa particularly in the eastern region where the impact of population differences on EFV PKs partly due to genetic and environmental variations is well-documented.[22,27]

Therefore, the overall objective of this study was to investigate the effect of pharmacogenetics and non-genetic factors on the population PKs of EFV through the development of a population-based PK/pharmacogenetic model in 100 HIV-infected Ethiopian children.

MATERIALS AND METHODS

Study participants and ethical considerations

A total of 100 children between 3 and 16 years old were recruited and enrolled from seven hospitals' ART centers found in two regional states of Ethiopia (Oromia and Southern Nations Nationalities and Peoples Regional states). These regions have the largest ethnic diversity and home for almost all ethnic groups in the country. The study participants were cART naive and received EFV-based cART. Initially, 30 and 90 subjects for rich and sparse PK sampling, respectively, were deemed adequate for the precise estimation of PK parameters without bias. However, only 13 and 87 subjects were willing to participate for trich and sparse PK sampling. Ethical approval was obtained from Addis Ababa University College of Health Sciences Institutional Review Board (Protocol No: 053/16/Pharma), and the National Research Ethics Review Committee, Ministry of Science and Higher Education-Ethiopia (Ref No: 3.10/166/2016). For all participants less than or equal to 12 years old, written informed consent was obtained from their parent or guardian, whereas for participants greater than 12 years of age, both informed consent from the parent or guardian and assent from the children were obtained.

Blood sampling

Blood samples for quantification of EFV plasma levels were obtained from 13 children after the first dose, and nine of them had additional blood samples collected at week 8 after starting EFV-based cART. Blood samples were collected at 0, 2.5, 16, and 24 h after dose from these subjects. Blood samples were also collected from an additional 87 participants at weeks 4, 8, 12, 24, and 48 after the start of EFV-based cART. From these additional subjects, single, mid-dose PK samples were collected between 8 and 16 h postdose in the scheduled weeks.

Determination of efavirenz plasma concentration

Plasma EFV was quantified by reversed phase high-performance liquid-chromatography tandem mass spectrometry (HPLC-MS/MS) detection, as described previously.[28] Analysis was done on Waters Acuity Ultra Performance LC-system, MS: Xevo TQ-S Micro. The lower limits of quantification in plasma were 15.78 ng/mL. The EFV calibration range was 15.78–15,783.75 ng/mL.

Genotyping

Genomic DNA was extracted from whole blood samples' leukocytes using QIAamp DNA Midi kit (Qiagen GmbH) according to the manufacturer's instructions. Common functional variant alleles in five genes (*CYP2B6*, *CYP3A5*, *ABCB1*, *SLCO1B1*, and *UGT2B7*) relevant for EFV disposition were selected and genotyped. Genotyping was conducted with real-time polymerase chain reaction using predeveloped Taqman assay reagents for allelic discrimination (Applied Biosystems Genotyping Assay) as described previously.[29]

Population pharmacokinetic analysis

A population PK model for EFV was built using a nonlinear mixed effect modeling program (NONMEM, version 7.5.0). Pirana (version 2.9.9; https://www.certara.com/software/pirana-modeling-workbench/), was used as a graphical user interface for NONMEM, whereas PsN (version 5.2.6; https://uupharmacometrics.github.io/PsN/), and R statistical software (version 4.1.2; www.r-project.org) were used for model management, model execution, output generation, and interpretation of results.

The population PK model was developed by establishing suitable structural, stochastic, and covariate models. First order conditional estimation with interaction (FOCE-I) was used to estimate model parameters. Individual PK parameter (P_i) values were modeled as $P_i = P_{TV} \times e^{\eta}$, whereby, P_{TV} is typical population parameter value and η (ETA) is randomly sampled from a normal distribution with mean of 0, and variance of ω^2 (i.e., $\eta_i = N(0, \omega^2)$). Additive, proportional, combined proportional plus additive error models were explored to account for within subject variability, experimental errors, and model misspecification. Improvements in model fit, based on goodness-of-fit (GOF) plots, were considered statistically significant if model objective function value (OFV) dropped greater than or equal to 3.84 (equivalent to p value $\leq = 0.05$ for χ^2 distribution). Precision of model parameters,

as measured by relative standard errors (RSE%) and 95% confidence intervals (CIs), were assessed using asymptotic standard errors (NONMEM $COV routine) or bootstrap CIs for the final model. Interindividual variabilities (IIV) of PK parameters, as measured by coefficient of variation (CV%), were calculated from ω^2 using the formula: $CV\% = 100 \times \sqrt{e^{\omega^2} - 1}$. A covariate model was developed through stepwise addition of covariates. Continuous and categorical covariates were added using the formular, $P = TVP \times \left(COV/COV_{median}\right)^{\beta}$, and $P = TVP \times \beta^{COV}$, respectively, where P is individual PK parameter, TVP is the typical population value of P, COV is covariate, taking values of 0 or 1 for categorical covariates, and β is the estimated covariate effect. The following covariates were explored for covariate model development; genotypes of EFV metabolizing enzymes (*CYP2B6*6*, *CYP3A5* [**3,*6,*7*], and *UGT2B7c.372G>A*) and drug transporters (*ABCB1c.3435C>T*, *ABCB1 c.4036A>G [rs3842]*, and *SLCO1B1*1B*, *SLCO1B1*5*, *SLCO1B1.rs4149032*), demographics (age and sex), baseline laboratory values (AST, ALT, ALP, total cholesterol, UREA, total bilirubin, estimated glomerular filtration rate [eGFR], plasma albumin, hemoglobin, hematocrit, LDL, HDL, triglycerides, viral load, and CD4 counts) and baseline clinical characteristics (use of isoniazid preventive therapy, hepatitis C infection, hepatitis B surface antigen, cotrimoxazole prophylaxis, pulmonary tuberculosis disease [PTB], WHO HIV stage, and ART regimen). Potential covariates were identified through visual exploration of ETA versus covariate plots, but only covariates with visual trend and with biological plausibility were further tested in the model. Covariates were retained in the model if their addition led to greater than or equal to 3.84 decrease in OFV (i.e., p value ≤0.05). Mixture modeling was used to find any unknown subpopulations whose typical parameter estimates might differ from that of the main population. The final model was qualified through visual inspection of GOF plots, prediction-corrected visual predictive check (pcVPC) to compare simulated versus observed concentrations, and bootstrap resampling of data and estimation to get nonparametric CIs of parameter estimates (Bootstrap CIs).

The final model was used to predict steady-state EFV concentration in virtual pediatric samples treated with EFV according to the SUSTIVA drug label. Two hundred (200) virtual pediatric samples (age <16 years) were sampled from the National Health and Nutrition Examination Survey (NHANES) database (https://wwwn.cdc.gov/Nchs/Nhanes/; spanning from 2001 to 2018) with stratification for age and weight-bands. For each sample, the proportions of the *CYPB6*6* genotypes were 45%, 45%, and 10% for *CYP2B6 *1/*1*, *CYP2B6 *1/*6*, and *CYP2B6 *6/*6*, respectively, whereas the proportions of the *ABCB1c.4036* genotypes were 20% and 80% for *ABCB1c.4036G/G* and *ABCB1c.4036G/A* or *ABCB1c.4036A/A*, respectively. The virtual subjects were also randomly assigned to an unknown subpopulation at the probability of 8% (see the Results section). For each sample, weight-band, and *CYP2B6*6* genotype, summary statistics (2.5th, 25th, 50th, 75th, and 97.5th percentiles) of EFV concentration at 12 h after dose were calculated. The summary statistics of the samples were subsequently used to compute population summary statistics (i.e., medians of the 2.5th, 25th, 50th, 75th, and 97.5th percentiles). Similar simulations were repeated after adjusting the dosage of EFV in subjects with CYP2B6*6/*6.

RESULTS

Subject characteristics

Table 1 presents descriptive statistics of demographic, clinical, and laboratory characteristics of the study subjects. Most subjects were aged below 12 years, with median age, weight, and body mass index for age percentile of 9 years, 22 kg, and 10, respectively. The subjects had relatively normal liver and renal function; immunocompetent levels of CD4 count; and some of them were on prophylaxis with isoniazid and cotrimoxazole. Most subjects received weight-based EFV dosing, as recommended in the SUSTIVA label, except for few individuals who received higher doses than recommended (Tables S1–S3).

Population pharmacokinetic model

The final dataset for population PK analysis included 554 PK samples collected over a span of 1 year (Figure 1). The base model (structural and stochastic models) was developed through several steps: the first step identified a one-compartment model parameterized in oral clearance (CL), oral volume of distribution (V) and absorption rate constant (K_a). At this step, the proportional residual error model adequately described the residual variability of EFV concentration and all IIVs of PK parameters were estimated. Results of the first step indicated poor precision in the estimation of K_a, IIV of V, and IIV of K_a (RSE >50%). In the second step, IIV of K_a was fixed to 0 without worsening model fit, but fixing IIV of V to 0 worsened model fit (ΔOFV = +6). Despite the worsening, IIV of K_a and IIV of V were fixed to 0 in the third step, where CL and V parameters were allometrically scaled by body weight using the power model equation (i.e., $CL_i = CL_{pop} \times \left(\frac{WT}{22}\right)^{0.75}$, $V_i = V_{pop} \times \left(\frac{WT}{22}\right)$). Allometric scaling led to improvement in the model fit (ΔOFV = −16.4). At the fourth step, IIV of V was

TABLE 1 Demographics, clinical, and laboratory characteristics of the study participants.

Characteristics	Levels	Values
Age, years, median (IQR)		9 (6–13)
Weight, kg, median (IQR)		22.05 (16.8–28.25)
Height, cm, median (IQR)		125 (106.5–140)
BMI, kg/m^2, median (IQR)		14.7 (13.401–15.9)
BMI for age percentile, median (IQR)		10 (1–29)
Aspartate aminotransferase, units/L, median (IQR)		37 (29–48)
Alanine aminotransferase, units/L, median (IQR)		27 (20–36)
Alkaline phosphatase, units/L, median (IQR)		274 (165–410)
Total cholesterol, mg/dL, median (IQR)		122 (98–155)
Blood urea nitrogen, mg/dL, median (IQR)		17.5(13.5–25.5)
Total bilirubin, mg/dL, median (IQR)		0.7 (0.41–1)
Creatinine, mg/dL, median (IQR)		0.54 (0.41–0.7)
eGFR, ml/min/1.73 m^2, median (IQR)		95.453 (70.7–115.7)
Albumin, mg/dL, median (IQR)		3.8 (3.4–4.2)
Hemoglobin, mg/dL, median (IQR)		12.5 (11.7–13.5)
Hematocrit, %, median (IQR)		38 (35.8–41.2)
Low-density lipoprotein, mg/dL, median (IQR)		45 (32–63)
High-density lipoprotein, mg/dL, median (IQR)		48 (39.075–66.3)
Triglycerides, mg/dL, median (IQR)		106 (87–162)
Viral load, copies/mL, median (IQR)		14,967 (1986–64,047)
CD4 count, cells/dL, median (IQR)		330 (200.5–671)
Sex, *n* (%)	Male	58 (58)
	Female	42 (42)
*CYP2B6*6* genotype, *n* (%)	*1/*1	45 (45)
	*1/*6	45 (45)
	*6/*6	8 (8)
	Missing	2 (2)
CYP3A5 number of functional alleles (**1*), *n* (%)	zero	54 (54)
	one	38 (38)
	two	6 (6)
	Missing	2 (2)
ABCB1 c.3435C>T, *n* (%)	C/C	65 (65)
	T/C or T/T	32 (32)
	Missing	3 (3)
ABCB1c.4036A>G (rs3842), *n* (%)	G/G	17 (17)
	G/A or A/A	80 (80)
	Missing	3 (3)
SLCO1B1 number of functional allele (*1), *n* (%)	zero	73 (73)
	one or two	24 (24)
	Missing	3 (3)
UGT2B7c.372G>A, *n* (%)	G/G	28 (28)
	A/G or A/A	69 (69)
	Missing	3 (3)
Hepatitis B virus antibody, *n* (%)	No	91 (91)
	Missing	9 (9)

(Continues)

TABLE 1 (Continued)

Characteristics	Levels	Values
Hepatitis B virus surface antigen, *n* (%)	No	90 (90)
	Yes	1 (1)
	Missing	9 (9)
Cotrimoxazole prophylaxis, *n* (%)	No	21 (21)
	Yes	69 (69)
	Missing	10 (10)
Pulmonary tuberculosis, *n* (%)	No	83 (83)
	Yes	15 (15)
	Missing	2 (2)
WHO clinical stage, *n* (%)	Stage 1	40 (40)
	Stage 2	22 (22)
	Stage 3	30 (30)
	Stage 4	5 (5)
	Missing	3 (3)
ART regimen, *n* (%)	TDF/3TC/EFV	53 (53)
	Abc/3TC/EFV	1 (1)
	AZT/3TC/EFV	13 (13)
	Missing	33 (33)

Abbreviations: 3TC, lamivudine; Abc, abacavir; ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; EFV, efavirenz; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TDF, tenofovir; WHO, World Health Organization.

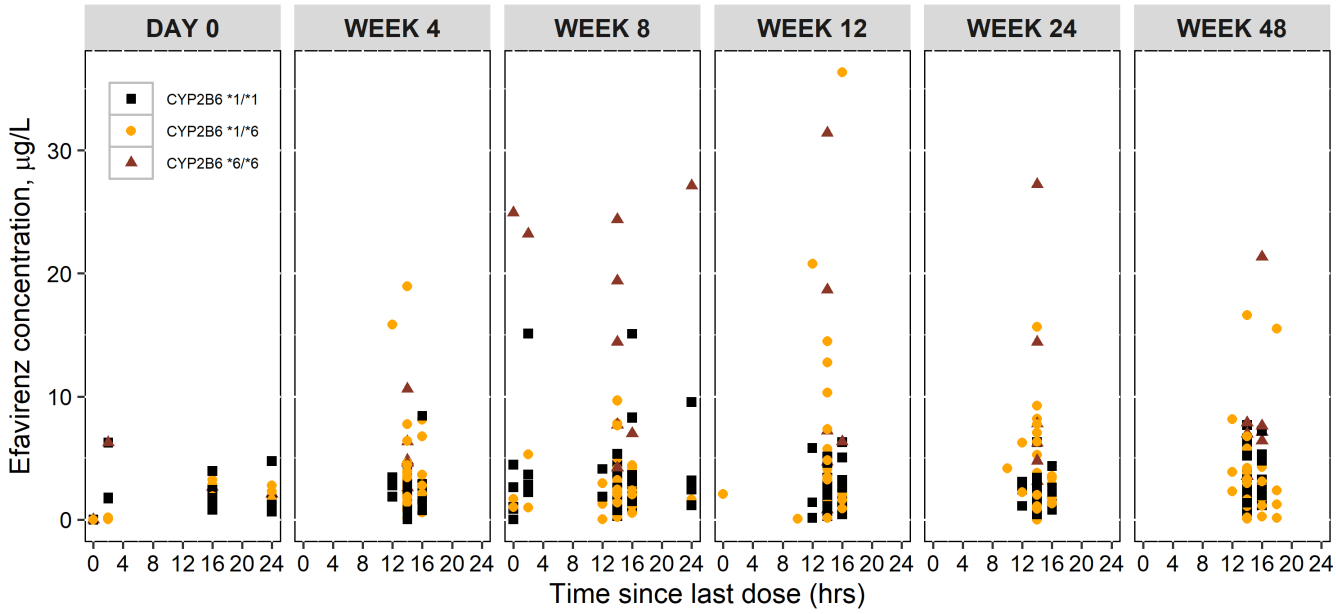

FIGURE 1 Observed efavirenz (EFV) concentrations over time since last dose stratified by day/weeks since initiation of EFV-based antiretroviral therapy (ART).

re-estimated resulting in some decrease in OFV by only 2.84 units (ΔOFV = −2.84). At this step, the inclusion of IIV of bioavailability (*F*) caused the IIV of *CL* to become 0 (ΔOFV = −12). This implied that, due to data sparseness, the IIV parameters of *CL* and *F* were unidentifiable. Because our goal was to determine predictors of EFV *CL*, subsequent models omitted IIV of *F*. At the fifth step, a sensitivity analysis was conducted to assess the practical identifiability of K_a. At this step, K_a values estimated in step 4 was decreased by 10-fold and fixed or increased by five-fold

TABLE 2 Parameter estimates of the final population PK model.

Parameters	Estimates (RSE)	Bootstrap median (95% CI)
Model conditional number	46.4	
CL (L/h)	4.30 (13%)	4.30 (3.20–5.30)
*V*c (L)	123.80 (10%)	125.24 (103.30–163.80)
K_a (/h)	0.78[a]	–
Proportional residual error (%CV)	50% (4%)	0.49 (0.45–0.54)
Fraction of typical CL for subjects with CYP2B6*1/*6	0.72 (11%)	0.73 (0.59–0.89)
Fraction of typical CL for subjects with CYP2B6*6/*6	0.28 (17%)	0.28 (0.2–0.46)
Fold of typical CL for subjects with ABCB1.rs3842 G/A or A/A genotype	1.45 (12%)	1.47 (1.15–1.87)
Proportional increase in CL from ≥12-weeks for subjects with CYP2B6*1/*1	0.12 (71%)	0.12 (0.001–0.27)
Proportional increase in CL from ≥8 weeks for subjects with CYP2B6*1/*6	0.23 (39%)	0.23 (0.07–0.40)
Proportion of an unknown subpopulation among the studied population	0.075 (71%)	0.09 (0.014–0.272)
Fraction of typical of CL for the subpopulation compared to the studied population	0.28 (36%)	0.29 (0.13–0.535)
Interindividual variability for CL (%CV)	35.4 (13%)	0.105 (0.05–0.169)
ETA shrinkage for CL (%)	20.7	–

Abbreviations: CI, confidence interval; *CL*, clearance; CV, coefficient of variation; K_a, absorption rate constant; PK, pharmacokinetic; RSE, relative standard error; Vc, apparent central volume of distribution.

[a]Fixed to this value.

and fixed. Both decreasing and increasing K_a values resulted in worsening of the model fit. In subsequent models, K_a was fixed at the value estimated at step 4. The results from the base model development steps are presented in Tables S1–S3.

Stepwise additions of *CYP2B6*6*, *ABCB1c.4036A>G*, and *ABCB1c.3435C>T* genotypes as covariates for *CL* resulted in −28.5, −12.1, and −1.2 units decrease in OFV, respectively. Therefore *CYP2B6*6* and *ABCB1c.4036A>G* were retained in the model. ETA versus covariate plots indicated sex, eGFR, and PTB could be potential covariates, but their inclusion into the model did not improve the fit.

EFV is known to auto-induce its own metabolism, therefore, the next step in covariate model development was to explore changes in EFV *CL* overtime. For this purpose, changes in clearance at weeks 4, 8, 12, and beyond week 24 were estimated. This was done in three steps. In the first step, changes were assumed to be independent of *CYP2B6* genotype. The model objective function decreased by 12 units, but the estimated *CL* changes were not statistically significant. In the second step, *CYP2B6* genotype-dependent changes in *CL* over time were estimated. For *CYP2B6*1/*1* genotype, the differences in *CL* between week 1 and week 4 onward or week 8 onward was not statistically significant, but the difference between week 1 and week 12 onward was statistically significant, albeit with large uncertainty (ΔOFV = −4.46, RSE = 56%). For *CYP2B6*1/*6* genotype, the difference in *CL* between week 1 and week 4 onward was not statistically significant, but the difference between week 1 and week 8 onward was statistically significant (ΔOFV = −8.16, RSE = 38%). No changes in *CL* over time were observed for *CYP2B6*6/*6* genotype. In the third step, to account for the potential impact of concomitant medications and variations in food co-administration, interoccasion variability in *CL* was explored and found to be negligible; occasions were defined as PK sampling occasions i(.e., weeks 0, 4, 8, 12, and ≥24).

A histogram of ETA for *CL* showed a bimodal distribution indicating the presence of two subpopulations with distinct typical *CL* (Figures S1–S3). To improve the model fit further, mixture modeling was conducted to estimate the proportions and the typical *CL* of the two subpopulations. This resulted in a statistically significant improvement in model fit (ΔOFV = −12; Table S3).

The final population PK model parameters and bootstrap CIs are presented in Table 2. The narrow bootstrap CIs are consistent with the small asymptotic RSE, indicating that the parameters were estimated with good precision. The estimates of population average total apparent clearance (*CL/F*), volume of distribution (*V/F*), and K_a were 4.3 L/h, 124 L, and 0.776/h, respectively, for typical 22 kg children with *CYP2B6*1/*1* and *ABCB1 c.4036G/G* genotypes. Our estimate for K_a is comparable to values reported previously, which range between 0.41 and 1.3 h.[16,17,26,30–32] The estimate of IIV of *CL* was 35.4%. For *V* and K_a, IIVs could not be estimated with reasonable precision and were therefore fixed to 0. The identified covariates of *CL* were body weight, *CYP2B6*6*

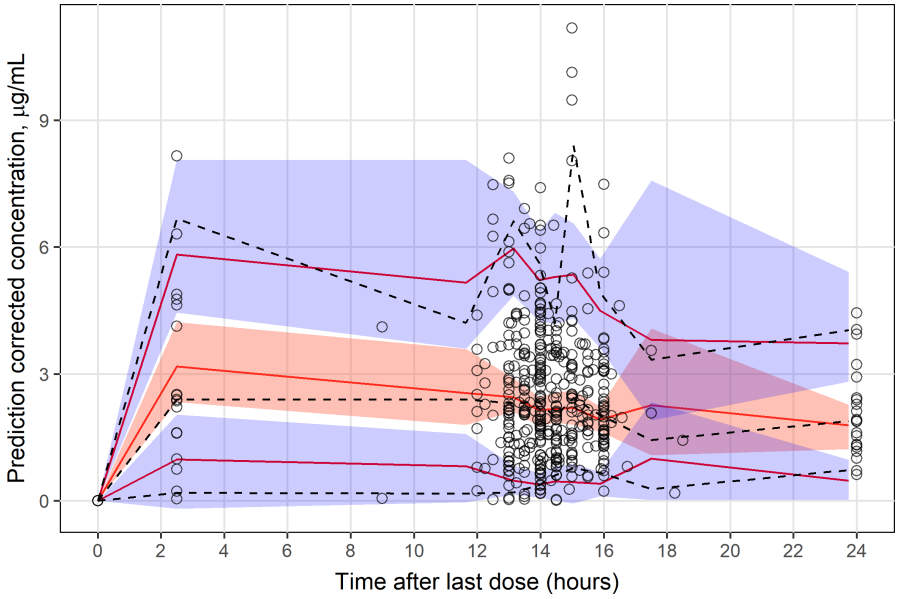

FIGURE 2 Prediction corrected visual predictive check (pcVPC) of the final population pharmacokinetic model. The dashed and solid lines represent 5th, 50th, and 95th percentiles of the observed and simulated data, respectively. The shaded areas represent 95% confidence interval of the 5th, 50th, and 95th percentiles of the simulated data.

genotype, *ABCB1 c.4036A>G* genotype, and greater than 12 or 8 weeks on treatment for *CYP2B6*1/*1* or *CYP2B6*1/*6*, respectively. An unknown subpopulation that makes about 7.5% of the studied population was identified and has about three-fold lower *CL* than the typical population. Based on the estimated covariate coefficients, individual subject clearance can be calculated from Equation 1. The GOF plots (Figure S2) and the pcVPC (Figure 2) of the final population PK model shows that the model provides adequate description of the observed PK data from the present study.

Equation for calculation of individual subject clearance based on the population PK parameter estimates: CL_i = individual predicted clearance; CL_{pop} = population average *CL*; *WT* = individual body weight; η = interindividual random effect; *f1* = if *CYP2B6*1/*6*; *f2* = if *CYP2B6*6/*6*; *f3* = if ABCB1.rs3842GA or AA; *f4* = if greater than 12 weeks and *CYP2B6*1/*6*; *f5* = if greater than or equal to 8 weeks and *CYP2B6*1/*6*; and *f6* = for a subpopulation of children.

$$CL_i = \left(4.3_{(CL_{pop})} \times \left(\frac{WT}{22} \right)^{0.75} \times 0.72_{(f1)} \times 0.28_{(f2)} \times 1.45_{(f3)} \times 1.12_{(f4)} \times 1.23_{f5} \times 0.28_{(f6)} \times e^{\eta} \right) \quad (1)$$

Based on the final model, the Monte-Carlo simulations indicated that EFV concentrations at 12-h after dose are comparable across the dosing weight bands in the SUSTIVA label (Figure 3). However, subjects with *CYP2B6 *6/*6* have relatively higher EFV concentrations compared to other genotypes with greater than 80% of those subjects having EFV concentrations greater than 4 µg/mL (Figure 3). On the other hand, greater than 80% of subjects with *CYP2B6*1/*1* or *CYP2B6*1/*6* who receive EFV dosing according to the SUSTIVA label, are predicted to have EFV concentration greater than or equal to 1 µg/mL.

Because EFV oral *CL* is reduced by approximately three-fold in subjects with CYP2B6*6/*6, EFV dosage in these subjects can be reduced by three-fold to achieve a comparable area under the curve (AUC), as in subjects with CYP2B6*1/*1. However, because the smallest dosage form and strength is a 50 mg capsule, EFV dosage can only be adjusted in multiples of 50 mg. For this reason, 12-h EFV levels were simulated after 50-, 100-, 150-, and 200-mg dose in CYP2B6*6/*6 subjects weighting 3.5–14.9, 15–32.49, 32.5–40, and greater than 40 kg, respectively, and compared with levels simulated in subjects with CYP2B6*1/*1 and CYP2B6*1/*6 receiving the labeled dose. The results indicated comparable 12-h EFV levels across genotypes for subjects weighing greater than or equal to 5 kg. For subjects under 5 kg, greater than 50% of subjects with CYP2B6*6/*6 still had 12-h EFV levels greater than 4 µg/mL (Figure S3).

DISCUSSION

Despite the adoption of the US Food and Drug Administration (FDA) and the WHO recommendations for EFV dosing in pediatrics, EFV exposures and ART

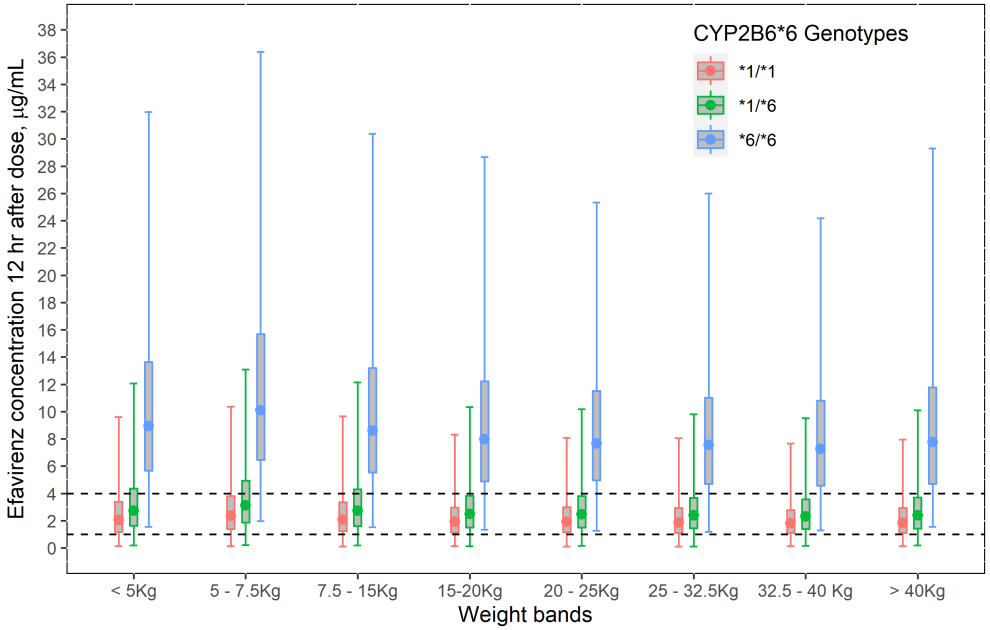

FIGURE 3 Boxplot of computed population summary statistics of the efavirenz (EFV) concentration at 12-h after dose. The lower and upper box hinges represent interquartile range (i.e., 25th and 75th percentiles), whereas the lower and upper whiskers of the error-bars represent 2.5th and 97.5th percentiles. The points in the middle of the boxes represent medians.

outcomes still vary widely in children.[33,34] EFV concentrations less or greater than certain thresholds have been associated with treatment failure or central nervous system adverse events, respectively. Such undesirable treatment outcomes can be avoided through cost-effective methods of medication management tailored to the causes of the variations. This study has identified different sources of EFV PK variation and therefore provides information that can be leveraged to devise appropriate management of EFV dose in pediatric patients.

Although some of the identified sources of EFV PK variability in this study were also identified previously, our findings add some unique information to EFV dosing armamentarium, particularly for Ethiopian pediatric subjects. First, our finding that subjects with *CYP2B6*6/*6* and *CYP2B6*1/*6* genotypes have typical EFV *CL* that is respectively 3.6-fold and 1.4-fold lower than subjects with *CYP2B6*1/*1* genotype, differs from that estimated in some of the previous pediatric studies which either reported about 2.5–3-fold lower *CL*[15,31,32,35] or greater than or equal to five-fold lower *CL*[26,36] for subjects with *CYP2B6*6/*6*. Furthermore, the finding indicates that the impact of *CYP2B6*6* on EFV PKs is higher in children compared to adult Ethiopians, as Habtwolde et al. estimated, about two-fold lower EFV *CL* for adults with *CYP2B6*6/*6*.[37] Second, consistent with previous studies in adult subjects,[11,22,23] this study finds that *ABCB1 c.4036A>G* (rs3842) genetic polymorphism has a significant impact on EFV PKs, a finding which to our knowledge has not been reported previously in pediatric subjects. Third, consistent with results from previous pediatric and adult studies,[5,6,15] this study demonstrates EFV autoinduction phenomenon in pediatric subjects. Fourth, in addition to the measured subject characteristics, our analysis has identified a subpopulation of Ethiopian pediatric patients with three-fold lower EFV *CL* than typical subjects. The subpopulation might represent unstudied covariates like other *CYP2B6* and *CYP2A6* polymorphisms. Last, unlike some of the previous EFV PK analyses in pediatrics,[32] given the narrow range of pediatric body weights, the allometric scaling of *CL* and *V* was implemented with allometric exponents fixed to theoretical values of 0.75 and 1 for *CL* and *V*, respectively, thus supporting the principle of allometry (weight-based scaling of physiological parameters). These interstudy differences highlight the importance of population-specific medication management to improve treatment outcomes.

In fact, various strategies for the management of EFV dose in adult and pediatric patients have been proposed and are in use. One of such the strategies is dose individualization to put EFV concentration within a therapeutic range. With such strategy, mid-dose, or trough EFV concentrations are compared with previously proposed therapeutic ranges, and individual doses are adjusted accordingly (i.e., therapeutic drug monitoring [TDM]).[15,33] Alternatively, different institutions and researchers have recommended different EFV doses based on identified source/s (covariate/s) of EFV PK variation to ensure that EFV concentrations are within acceptable limits (e.g., a therapeutic range) across different values of the

covariates.[33,38,39] However, an additional, but less studied, method of medication management is dose modification based on ART outcomes, like in the case of drug holidays due to EFV toxicity.[40,41] Although plasma EFV concertation 1–4 μg/mL is widely accepted as the therapeutic range,[42] viral susceptibility has been identified as an important determinant of the threshold for therapeutic concentrations with a possibility of lower thresholds for efficacy.[43–45] Furthermore, sensitivity to EFV toxicity seems to vary widely with some subjects tolerating greater than 4 μg/mL, whereas others have an increased likelihood for EFV toxicity with EFV trough levels greater than 2.74 μg/mL.[46,47] This implies that toxicity-guided EFV dose reductions may provide safer personalized doses which maintain viral suppression.[48] Our findings provide support for an additional layer of EFV dose management. Although body weight and *CYP2B6* genetic polymorphism are commonly considered for EFV dose recommendations, there are other covariates that significantly impact EFV exposure and possibly treatment outcomes. For this reason, additional medication management for EFV are warranted.

Routine management of EFV doses in pediatric patient has the potential of decreasing incidences of EFV toxicity, poor adherence, and treatment failure. However, genotype or TDM-based dose optimizations is not feasible in resource limited settings as these methods require expensive equipment, consumables, and skilled labor, which may be unavailable in such settings. Therefore, in resource limited settings, EFV dose adjustments based on adverse outcomes may be a cost-effective strategy. EFV dose can be tapered in steps until EFV toxicity is completely alleviated. However, the efficacy of this practice needs to be confirmed through future clinical studies.

In this study, the estimated PK parameters and the consequent Monte Carlo simulations indicate that greater than 80% of the studied population with *CYP2B6*1/*1* or **1/*6* genotypes achieved the 12-h EFV concentration that is above the suggested therapeutic threshold of 1 μg/mL. This is comparable with findings by Bienczak et al., who reported that among Uganda and Zambian children with *CYP2B6*1/*1* genotype greater than 20% had 12-h EFV concentrations that were less than or equal to 1 μg/mL.[16] This similarity is inconsistent with the difference in the estimated EFV *CL/F* between this study (typical value (95% CI) = 10.24 [7.6–12.6] L/h/70 kg) and that reported by Bienczak et al. (21.6 L/h/70 kg), and is driven by large residual error in our study (50% vs. 6.2%). In fact, the estimate of EFV *CL/F* in this study is at the lower end of the reported EFV *CL/F* in literature. According to the literature, the estimates of EFV *CL/F* in children with *CYP2B6*1/*6* vary across studies ranging from the lower end of 11.2–14.5 L/h/70 kg[15,17,32] to the higher end of 16.1–25.2 L/h/70 kg.[16,26,31,33,34] This wide variation in EFV *CL/F* across populations can presumably be explained by differences in EFV bioavailability across studies and also by other genetic variations in EFV metabolizing enzymes.[16,19,25]

Our study has some limitations. One of the limitations is that genetic variations in other metabolic pathways, including *CYP2A6* and *CYP3A4*, were not assessed, although the contribution of these enzymes for EFV metabolic disposition is considered minor. Whereas some studies indicated the significance of *CYP2A6* and *CYP3A4* genotypes,[19,25] others showed that their effect is minimal.[49] Moreover, EFV plasma concentration is mostly impacted by *CYP2B6* genetic polymorphisms, especially the *CYP2B6*6 (c.516G>T),* which is the most common single-nucleotide polymorphism in Sub-Saharan Africans.[49,50] A second limitation is that we did not consider the effect of food co-administration. Food is known to increase EFV bioavailability.[39] In this study, although patients were instructed to administer EFV with food, it was not possible to monitor compliance to this recommendation due to the long study follow-up duration (spanned over a year). A third limitation is that, although the study was planned for rich and sparse PK sampling in 30 and 90 subjects, respectively, only 13 and 87 subjects were willing to participate. Consequently, data sparseness did not allow for estimation of IIVs of other parameters than *CL*. Last, most of the variability in observed EFV levels remain unexplained in the residual error model; this is probably due to unaccounted poor adherence, incorrect dosing and sampling time records, and bioanalytical errors. Despite the large residual error, the estimated PK parameters are consistent with those reported in previous literature. The recommended genotype-based dosage adjustments are based on the estimated typical parameter values and, therefore should be reliable in practice. The residuals and between-subject variabilities have impact on the distribution of the predicted plasma concentration at 12-h after dose. This distribution should represent the expected distribution in the real world, especially in the community where the study was conducted.

AUTHOR CONTRIBUTIONS

A.C., E.N.K., and E.A. wrote the manuscript. A.C., B.T.T., T.E.C., E.M., and E.A designed the research. A.C., B.T.T., T.E.C., E.M., and E.A. performed the research. A.C., J.H.A., and E.N.K. analyzed the data. E.N.K., J.H.A., and E.A. contributed new reagents/analytical tools.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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